REMARKS

Status of the Claims

By the present communication, claims 1-32 and 45-48 have been canceled and new claims 53-71 added. No new matter is introduced by these amendments as the new claims correlate to canceled claims as indicated below:

New Claim(s)	Canceled Claim(s)
Claim 53	Claim 1
Claims 54-55	Claim 4
Claims 56-57	Claims 7-8
Claim 58	Claim 21
Claim 59	Claim 45
Claims 60-61	Claims 22-23
Claim 62	Claim 10
Claims 63-70	Claims 12-19
Claim 71	Claim 47

Thus, the claimed subject matter is fully supported by the specification and claims as originally filed. Applicant reserves the right to pursue any subject matter that is canceled by the instant amendment in future prosecution of this application or in future divisional or continuation applications. Upon entry of this amendment, claims 53-71 are pending, with claims 53-59 under consideration.

Claim Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-9, 20, 21, 47, and 48 were rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter the Applicant regards as the invention. New claims 53-57, and 71 correlate to the rejected claims.

As a first basis of rejection, the Office has asserted that it is not clear what is intended by reference in the claims to a functional fragment of hnRNP K. By way of the instant amendment, all reference to functional fragments of hnRNP K have been removed from the pending claims, thus rendering this basis of rejection moot.

As a second basis of rejection, the Office has asserted that claim 47 is further indefinite due to its dependence from previously canceled claim 8. The dependency of claim 47 from claim 8 was a typographical error which has been corrected by way of the instant amendment. New claim 71 now depends from claim 58 (which correlates to previously withdrawn claim 10) and has been withdrawn from consideration, thus rendering this basis of rejection moot.

Applicants respectfully submit that the rejections under 35 U.S.C. § 112, second paragraph have been rendered moot by amendments submitted herewith and should therefore be withdrawn.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Enablement

Claims 1-9, 20, 21, 45, 47, and 48 stand rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does not reasonably provide enablement for methods of modulating viral load of or treating infection by any hepatitis virus through any modulation of hnRNP K and a regulatory region of the genome in the target hepatitis virus. New claims 53-59 and 71 correlate to the rejected claims.

By way of this amendment, all pending claims have been amended to refer to methods of reducing viral load of or treating infection by human Hepatitis B. The Office has recognized that such methods are enabled by the instant specification. Office Action mailed February 24, 2010, p. 4, third paragraph, and p. 6, first paragraph. As such, Applicants respectfully request withdrawal of the enablement rejections.

Written Description

Claims 1-9, 20-21, 45, and 47-48 stand rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does comply with the written description requirement. New claims 53-59 and 71 correlate to the rejected claims. By way of the instant amendment, claim 71 has been withdrawn from consideration.

As a first basis for rejection, claims 1-9, 20-21, 45, and 47-48 were rejected as lacking adequate support for the inhibition of complex formation between hnRNP K and any regulatory region of any Hepatitis virus. As indicated above, all pending claims have been amended to refer to methods of reducing viral load of or treating infection by human Hepatitis B. The claims have been also been amended to clearly indicate that reduction of complex formation occurs via administration of a nucleic acid which reduces the amount of hnRNP K in cells of the host organism. Applicants respectfully submit that the amended claims are fully supported by the specification.

For example, Example 6 on p. 31 demonstrates the effect of three different nucleic acids against hnRNP K (i.e., three different siRNAs) in HepG2 co-transfected cells. The nucleic acids against hnRNP K reduced the amount of hnRNP K in cells of the host organism (shown as a measure of hnRNP K mRNA in Figure 17, part I), which resulted in a reduction in complex formation between hnRNP K and the human Hepatitis B genome and hence human Hepatitis B replication (shown as a measure of HBV DNA in Figure 17, part II).

As a second basis for rejection, claims 1-9, 20-21, and 47-48 were rejected as lacking adequate support for the inhibition of complex formation between a functional fragment of hnRNP K and a Hepatitis virus genomic regulatory region. As indicated above, all pending claims have been amended to remove reference to functional fragments of hnRNP K, thus rendering this basis of rejection moot.

As a third basis for rejection, claims 1-9, 20-21, 45, and 47-48 were rejected as lacking adequate descriptive support for compounds that may be administered to effect the modulation of the hnRNP K viral regulatory region complex formation. As amended herein, all pending claims have been amended to indicate that complex formation is reduced by administration of a nucleic acid molecule against hnRNP K that results in reduction of the amount of hnRNP K in cells of the host organism.

Example 6, as described above, demonstrates the effect of three different nucleic acids against hnRNP K on HepG2 co-transfected cells. Administration of nucleic acids against hnRNP K reduced the amount of hnRNP K in cells of the host organism (shown in Figure 17, part I), which resulted in a reduction in complex formation between hnRNP K and the human Hepatitis B genome and hence human Hepatitis B replication (shown in Figure 17, part II). In fact, the Office has acknowledged that the specification provides support for such methods in the specification at Example 6, p. 31-32. Office Action, p. 10, second paragraph.

The Office further alleges that there is no specific indication of a region of hnRNP K that may be targeted. Applicant respectfully submits that this allegation is based on an assumption that an administered compound will interact with a region of hnRNP K to disrupt hnRNP K's binding capability. Instead, the amended claims require that the administered compound act to reduce the amount of hnRNP K in cells of the host organism. In Example 6, and Figures 16 and 17, the specification demonstrates that nucleic acids are useful in the instant methods to reduce complex formation between hnRNP K and the HBV genome, and thus HBV replication by means of reducing the amount of hnRNP K in cells of the host organism, and do not target a particular region of hnRNP K to disrupt hnRNP K's binding capability.

The Office also alleges that the application does not provide examples of DNA generally, or any specific aptamers that achieve the desired functions. Further, the Office alleges that the application does not provide any guidance as to what structures or DNA sequences may correlate with utility in the claimed methods. Applicants submit that it is well within the knowledge of a skilled artisan to produce suitable nucleic acid molecules, as antisense molecules in the range of this length have been demonstrated in the art. With regard to aptamers, Applicants submit that aptamers are known to be RNA or DNA molecules originating from *in vivo* selection experiments (i.e. SELEX, *see e.g.*, Jayasena, Clinical Chemistry, 1999, and Hermann and Patel, Science, 2000, submitted in an IDS herewith). As an aptamer is generated from a random sequence library, the skilled artisan does not require a given sequence, but rather requires merely the hnRNP K protein as a target in order to obtain aptamers via the SELEX process. Further, Applicants respectfully direct the Office's attention to five exemplary siRNA sequences described in Example 6 (SEQ ID NOs 3, 5, 7, 9, and 11) that are demonstrated as useful for reducing complex formation between hnRNP K and the HBV genome by means of reducing the amount of hnRNP K in cells of the host organism

Thus, Applicants respectfully submit that the amended claims are fully supported by the instant specification and respectfully request withdraw of the written description rejection.

Claim Rejections under 35 U.S.C. § 102

Claims 1-4, 6-9, and 47 were rejected under 35 U.S.C. § 102 as allegedly inherently anticipated by Rang et al. (JBC 277:7645-47) in light of the teachings of Zhang et al. (Cell Microbiol 10:112-121) and Bovine et al. (Hepatol 43:1364-74). New claims 53-57 and 71 correlate to the rejected claims. By way of the instant amendment, claim 71 has been withdrawn from consideration. Applicants respectfully submit that as amended herein, the pending claims are not anticipated.

All pending claims have been amended to refer to methods reducing viral load of or treating infection by human Hepatitis B virus in a host organism comprising administering a

nucleic acid molecule against hnRNP K. Rang et al. does not describe administering a nucleic acid molecule. Rather, Rang et al. merely describes treating cells with IFNα, a protein. Rang et al., p. 7645-46, left col., bridging paragraph (disclosing treatment of Huh7 and HEp2 cells containing human Hepatitis B virus with IFNα). Thus, Rang et al. does not anticipate the pending claims.

The Office notes that the later teachings in the art indicate that another protein (A3B) suppresses HBV replication through inhibiting the binding of hnRNP K to the enhancer II region of HBV. (Citing Zhang et al.). Zhang et al., however, shares the deficiency of Rhang et al. in that it does not describe administering a nucleic acid molecule. Rather, Zhang et al. suggests another protein (A3B) can suppress HBV replication. Further, Zhang, et al. does not provide any indication on the *in vivo* mechanism involved in suppressing human Hepatitis B virus DNA. Therefore, there is no indication that inhibiting HBV replication is occurring by reducing the amount of hnRNP K in cells of the host organism. Such contemplation can only be arrived at through the improper use of hindsight in light of the teachings of the instant specification.

Furthermore, the secondary reference cited by the Office do not provide sufficient evidence to conclude that the method of Rang et al. results in reduction of complex formation between hnRNP K and the human Hepatitis B virus genome by the reduction of hnRNP K as required by the instant claims. Figure 3A of Bonvin et al. shows that exposure to IFNα (the same protein used by Zhang et al.) at 1000 U/ml is required for 48 hours to achieve a significant increase in A3B levels in Huh-7 and HepG2 cells. Additionally, cotransfection of $A3B_L$ with HBV showed a reduction in HBV replication. However, this effect was not observed with $A3B_S$. Bovine et al., p. 1369, left col., second paragraph, lines 18-20).

In this regard, Bonvin et al. report an entirely different effect that well explains the observed reduction in HBV levels: induction of hypermutations (explained on Bonvin et al. p 1370). $A3B_L$ is an editing enzyme, and the differences observed by Bonvin in HBV replication upon exposure to $A3B_L$ and $A3B_S$ match the differences in editing activity of the two enzymatic isoforms. Thus, a skilled artisan would not likely conclude that complex formation between

hnRNP K and the HPV genome is significantly reduced by the reduction of hnRNP K through exposure to IFNα (the method of Rang et al.).

Additionally, the approach followed by Rang et al. further differs from the method defined in the instant claims in that Rang et al. does not disclose a host organism infected with human Hepatitis B virus, but rather cultured human cells. (p. 7645, right col. paragraph entitled "Cell Culture and Transfections").

Thus, Rang et al. does not anticipate the pending claims.

Applicants respectfully submit that the pending claims are in condition for allowance. In the event that any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any additional extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 07/23/10

By _____

FOLEY & LARDNER LLP
Customer Number: 30542
Telephone: (858) 847-6700
Facsimile: (858) 792-6773

Barry S. Wilson, Reg. No. 39,431
Attorney for Applicant